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Atypical right hemispheric functioning in the euthymic state of bipolar affective disorder

Pablo Najt & Markus Hausmann

Department of Psychology, Durham University, United Kingdom

Address for correspondence:

Pablo Najt

Clinical Neuroimaging Laboratory, School of Medicine, College of Medicine, Nursing and Health Science, National University of Ireland, Galway, Galway, Ireland

Phone: +353 914954565

Fax: +353 91494563

E-mail: pablo.najt@nuigalway.ie

Abstract

Bipolar disorder (BD) has been associated with right hemisphere dysfunction. These findings usually come from studies that have not distinguished between symptomatic and euthymic states of BD. The present study aims to investigate atypical right (and left) hemispheric functioning in euthymic BD patients. We evaluated 40 participants (18 healthy controls and 22 euthymic BD patients) using an emotional prosody dichotic listening task and a linguistic dichotic listening task which have been shown to produce a strong left ear advantage (LEA) and right ear advantage (REA), indicating a right and left hemisphere superiority, respectively. The results replicate the well-known LEA in emotional prosody for healthy controls. In contrast, no ear advantage was found for emotional prosody in euthymic BD patients. Both groups revealed the well-established REA in the linguistic dichotic listening task. The patient group was heterogeneous with regard to medication, as it consisted of patients with a variety of pharmacological treatments. The results are in line with previous studies in symptomatic BD patients, and suggest that atypical LEA in emotional prosody can be interpreted as a neurobehavioral vulnerability marker of emotional dysregulation and dysfunction in the right hemispheric fronto-temporal network in both symptomatic and euthymic BD patients.

Keywords: Dichotic listening; functional hemispheric asymmetries; emotional prosody; emotion regulation; euthymia;

1. Introduction

Bipolar disorder (BD) is a highly dynamic disorder with a cyclic pattern of mood states ranging from hypomania and moderate depression to severe mania or depression with psychotic features, as well as mixed states (Müller-Oerlinghausen et al., 2002). BD is associated with dysfunction of emotion regulation (Phillips et al., 2008), which involves the initial steps of perception of information eliciting emotional arousal.

Emotional dysregulation in BD has also been linked to atypical functional hemispheric asymmetries as shown by neuroimaging studies (Yurgelun-Todd et al., 2000; Foland et al., 2008; Killgore et al., 2008; Strakowski et al., 2011; Liu et al., 2012) suggesting a deviation from the typical right hemisphere advantage in emotion perception. For example, Killgore et al., (2008) found a decrease in right inferior orbitofrontal activation in BD patients with manic symptoms during passive viewing of a series of black and white fearful facial expressions. A similar pattern has been reported by Jogia et al., (2008), who found a reduced right ventrolateral PFC activation in BD patients with manic symptoms compared to healthy controls during recognition of sad facial expressions. Further evidence for right frontal dysfunction in mania has been suggested by an fMRI study revealing decreased right-sided activation in the dorsolateral region of the PFC in BD patients with manic symptoms while identifying fearful expressions in a facial emotion task (Killgore et al., 2000). These findings suggest that orbitofrontal and prefrontal areas in the right hemisphere are associated with a failure to inhibit emotional salience in BD patients during manic episodes.

Atypical functional hemispheric asymmetries in emotion perception have also been found in depressive BD patients. However, evidence here indicates left rather than right orbitofrontal and prefrontal areas (e.g., Lawrence et al., 2004; Altshuler et al., 2008). Specifically, Altshuler et al. (2008) found reduced left orbitofrontal activation in depressive BD patients compared to healthy controls in a match facial emotion task using neutral and negative expressions. Decreased activation in left dorsolateral prefrontal cortex has also been found in depressive BD patients for the perception of sad facial expressions (Lawrence et al., 2004). In line with these findings an electrophysiological study by Allen et al. (1993), found higher right than left frontal activation in depressive BD patients compared to healthy controls. Overall these studies suggest that the degree (and sometimes even the direction) of functional hemispheric asymmetries in BD patients change according to their manic and depressive episodes. These findings can be interpreted with respect to the Valence-Specific Hypothesis of emotion perception, which proposes left hemisphere specialization for processing positive emotions and right hemisphere bias for processing negative emotions (Ahern and Schwartz, 1979; Wedding and Stalans, 1985; Adolphs et al., 2001). According to this model, atypical functioning of the left hemisphere is related to an increase in negative emotional states whereas atypical functioning in the right hemisphere is related to increases in positive emotional states. Although mania can occur as a consequence of more positive and/or less negative emotions (Gruber et al., 2008; Gruber et al., 2011), studies of symptomatic BD suggest a state-dependent imbalance in positive and negative emotions, which probably relates to atypical functional hemispheric asymmetries. However, the causality of the relationship between (atypical) functional hemispheric asymmetries

and emotional states is still unclear. There is some evidence that changes in functional asymmetries relate to reorganization of the brain. Left hemisphere lesions are likely to induce a marked shift in hemispheric dominance for language. This has been suggested by verbal dichotic listening studies revealing atypical left ear advantage following left hemisphere lesion (Moore and Papanicolaou, 1988). Similarly, the left hemisphere might be more (or even dominantly) involved in typical right hemisphere processes (e.g., emotional prosody processing), if the functional organization in the dominant right hemisphere is dysfunctional. Therefore, atypical functional hemispheric asymmetries in BD may reflect a compensatory strategy for effective processing emotional prosody, and coping with mood symptoms in general (Rotenberg, 2004; Rotenberg, 2008). Such mechanism could involve recruitment of left or right frontal regions compensating for manic and depressive mood episodes, respectively. One could assume that manic and depressive mood changes lead to atypical functional hemispheric asymmetries in fontal areas. The latter has been shown by several mood induction studies in healthy subjects (e.g., Altenmüller et al., 2002; Flores-Gutiérrez et al., 2007). If atypical functional hemispheric asymmetries were also identified during euthymic states (the absence of depressed or elevated mood outside the normal range), this would challenge the idea that atypical functional hemispheric asymmetries in BD patients occur as a consequence of pathological mood states. Rather, this would imply that atypical functional hemispheric asymmetries constitute a vulnerability marker of BD.

Although only a few previous studies differentiated between symptomatic and euthymic BD patients (e.g., Wessa et al., 2007; Robinson et al., 2008; Chen et al., 2010; Keener et al., 2012), the majority of these studies also found atypical functional

hemispheric asymmetries in emotion perception involving the right fronto-amygdala network in symptom free BD patients. For example, Chen et al. (2010) reported increased activation in the right amygdala and right orbitofrontal cortex in euthymic BD patients relative to healthy controls during a facial emotion task in which participants were explicitly asked to rate the affective intensity of faces depicting one of six emotion types (happiness, sadness, disgust, fear, surprise, and anger). Atypical increase in right prefrontal activation in euthymic BD patients was also found with an emotional face matching task (Robinson et al., 2008), and an emotional go/no-go paradigm where subjects responded to a target emotional face (Wessa et al., 2007). Moreover, a recent fMRI study (Keener et al., 2012) in euthymic BD patients found an increase in activation of the right amygdala, especially in response to happy faces. The study's task required participants to label color flashes that were superimposed on dynamically changing background faces comprising morphs from neutral to angry, sad, fearful, or happy expressions. Emotional expressions were task irrelevant and therefore were only implicitly processed by participants. In line with the proposed predominant role of the right hemisphere in emotional processing (Borod et al., 1998), BD patients might have perceived emotional faces as more emotional than healthy controls. This might also explain the increased right hemisphere involvement in BD euthymia in this study. Also resting encephalogram in children with both parents and grandparents diagnozed with major depressive disorder showed greater alpha asymmetry, with relatively less right than left hemisphere activity, compared with children at lower risk for depression (Bruder et al., 2007). Although atypical right hemisphere functioning seems to be a trait characteristic associated with BD and major depression disorder, it is unclear whether this atypical functional hemispheric

asymmetry reflects dysfunction, or a compensatory/adaptive mechanism of these disorders.

A simple and reliable technique to study functional hemispheric asymmetries in emotional and non-emotional processing is the dichotic listening paradigm (Hugdahl, 2000; Voyer and Flight, 2001). In dichotic listening, a participant is simultaneously presented with two different auditory stimuli (usually speech) separately to each ear via headphones. After each trial, participants are asked to repeat the stimulus (usually one) they have identified. The dichotic listening paradigm typically shows a better reproduction of speech stimuli presented to the right ear (right ear advantage, REA; Hugdahl et al., 1999). Due to the predominantly contralateral projection in the auditory system (Kimura, 1967), the REA has been interpreted as indicating a left hemisphere advantage in language processing. Following the same logic, a left ear advantage (LEA) generally found for non-verbal stimuli, such as complex tones (e.g., Sidtis, 1981) and emotional prosody (e.g., Bryden and MacRae, 1989; Grimshaw et al., 2003), indicates right hemisphere specialization. A right hemisphere asymmetry in emotional prosody is also supported by CT and MRI studies, showing impaired emotional prosody comprehension in patients with right temporal posterior lesions (Gorelick and Ross, 1987; Ross, 1981; Ross and Monnot, 2008). In contrast, patients with left hemisphere lesions showed preserved emotional prosody comprehension (e.g. Blonder et al., 1991).

In line with atypical right hemisphere functioning in BD, two dichotic listening studies in symptomatic BD patients found a reduced LEA for processing complex tones (Bruder et al., 1989; Bruder et al., 1994). Bruder et al. (1994) tested BD patients during manic and again during euthymic states using the complex tone dichotic

listening task, in which participants were asked to discriminate pitch in a dichotic pair of complex tones. Here, BD patients revealed a reduced LEA during mania compared to healthy controls. During euthymia, however, the LEA was preserved, suggesting that a reduced right hemisphere advantage for the processing of complex tones is specific to symptomatic BD patients. Similarly, Bruder et al. (1989) found a reduced LEA in melancholic depressive BD patients in the complex tone dichotic listening task. Overall, these findings suggest that symptomatic BD patients show atypical functional hemispheric asymmetries due to right hemisphere dysfunction. However, none of these dichotic listening studies assessed emotional prosody in BD. For example, Bruder et al. (1994) used pitch of complex tones rather than emotional prosody as stimuli.

Another study assessed functional hemispheric asymmetries of speech processing in BD patients during manic episodes with psychotic symptoms, and euthymic episodes (Kaprinis et al., 1995). The study used a free-recall paradigm in which the listener was asked to repeat two different spoken digits, simultaneously presented to the right and left ear. The authors found that, similar to healthy controls, manic BD patients after recovery (i.e. euthymia) showed the expected REA. However, during manic states, the same BD patients showed an LEA, indicating an atypical right hemisphere advantage in speech processing. The authors hypothesized that this result may be explained by hyperactivation of the right hemisphere in symptomatic BD patients. Contrary to Kaprinis et al.'s findings, Bruder et al. (1994) found the expected REA in manic BD patients using a dichotic listening consonant vowel task involving verbal processing. Also, in contrast to Bruder et al., Kaprinis et al.'s study included BD patients with psychotic symptoms. Thus, a reduced left hemisphere advantage for

verbal processing might be related to psychosis rather than BD. In other words, similar to the fMRI studies reported above, dichotic listening findings also suggest that symptomatic BD patients show atypical functional hemispheric asymmetries. However, in order to investigate the idea that right hemisphere dysfunction is a correlate of BD, the present study aims to investigate functional hemispheric asymmetries in euthymic BD patients with an emotional/prosodic dichotic listening and a non-emotional/linguistic dichotic listening task. Both tasks have previously been shown to produce a robust LEA and REA, corresponding to right and left hemisphere advantages, respectively (Grimshaw et al., 2003). Based on the assumption that atypical functional hemispheric asymmetries underlying emotional processes can occur independently of manic or depressive mood states in BD, it is hypothesized that euthymic BD patients will show a reduced LEA in processing emotional prosody, whereas the REA for linguistic processing will be preserved.

2. Method

2.1 Subjects

Twenty-two patients (13 women) with BD (Age: 44.59 ± 9.97 years; means ± SD) were recruited from the Northumberland NHS Foundation Trust, and the Tees, Esk and Wear Valleys NHS Foundation Trust. The diagnosis of BD was confirmed by an independent psychiatrist. All the individuals fulfilled the following inclusion criteria: (1) a diagnosis of BD, type I, according to the Structured Clinical Interview for DSM-IV (SCID-P; First et al., 1995), (2) no current concomitant Axis I disorder, and (3) no history of medical or neurological condition. Individuals were also excluded if they

met the DSM-IV diagnosis for anxiety disorders or substance abuse within the preceding six months. Bipolar patients were clinically stable outpatients at the time of the study. Current depressive symptoms were assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960). Manic symptoms were assessed with the young mania rating scale (YMRS; Young et al., 1978).

As a group [HAM-D = 3.05 ± 1.98 (0–7) and YMRS = 5.18 ± 4.23 (0-10)] and based upon symptom ratings (HAM-D ≤ 7, YMRS ≤ 10), BD patients were euthymic on the day of the study. Anxiety symptoms were previously present in three of the patients. Nine out of the twenty-two BD patients had a prior diagnosis of psychotic disorder. Five patients had a history of alcohol or substance abuse. Fifteen of the bipolar patients were taking mood-stabilizing medications; eight patients were taking antidepressants. In addition, twelve patients received atypical antipsychotics. None of the BD patients experienced psychotic symptoms at the time of the assessment.

Eighteen healthy controls (Age: 45.11 ± 7.50 years; 9 women) were recruited through local announcements (e.g. local post office, community library, Durham University, etc.). Although BD patients and control participants were not individually matched for age, sex, and education, no significant group differences were found on these variables. Healthy controls had no history of any Axis I disorder and no history of affective disorder or schizophrenia in first-degree relatives.

Patients and controls reported no hearing difficulties, and were right-handed as determined with the Edinburgh Handedness Inventory (Oldfield, 1971). The asymmetry index provided by this test is calculated using the following formula: ((R-L)/(R+L)) x 100, resulting in values between -100 and +100. This range describes the continuum from extreme sinistrality to extreme dextrality. The handedness scores for

patients (88.99 ± 12.51) and controls (91.67 ± 9.85) did not significantly differ ($t(38) = 0.74$, n.s.). Participants characteristics are provided in Table 1.

All participants were compensated for participating in the study. The study was approved by the regional ethics committee from the NHS and Durham University Ethics Advisory Committee. After receiving a complete description of the study, written informed consent was obtained from each participant.

2.2 Procedure and Materials

The dichotic listening paradigm was identical to that described by Grimshaw et al. (2003). The experiment consisted of a linguistic and a prosodic dichotic listening task. The linguistic task was a word identification task, which required participants to recognize a particular word target, and typically generates a REA corresponding to the left hemisphere. The prosodic task required participants to recognize a particular emotional tone of voice, and this task typically generates a LEA corresponding to the right hemisphere. The stimuli set for both tasks consisted of four two-syllable words: "bower", "dower", "power", and "tower", each spoken by a male voice in angry, happy, neutral, and sad tones of voice (Bryden and MacRae, 1989). Both tasks consisted of four blocks of 72 trials, for a total of 288 trials (excluding 16 additional practice trials). Word target and voice target, as well as block order, were counterbalanced across participants. Target and block order were counterbalanced across subjects, resulting in 16 different block-target combinations (i.e., word target: bower, voice target: angry). Orientation of supraaural headphones with circumaural cushions was reversed across participants. The current study was not designed to

examine the stimulus valence, since the critical question was to investigate atypical hemispheric asymmetries in BD regardless of mood symptoms.

Participants were instructed to listen for either a word target or voice target, and respond as quickly and accurately as possible to whether or not they heard the target in either ear using the index and middle fingers on the "1" (present) and "2" (absent) keys of a computer keyboard. Each word or tone of voice was present in 50% of the trials, 25% in the left ear and 25% in the right ear. Participants responded to both the word target and the voice target for two consecutive blocks. The experiment was controlled by E-Prime (Psychology Tools Inc., Pittsburgh, PA) on a desktop PC. Response times and accuracy were recorded as dependent measures.

3. Results

3.1 Accuracy

The accuracy data were subjected to a 2 × 2 × 2 × 2 split-plot analysis of variance (ANOVA), with Task (linguistic/prosodic) and Ear (left/right) as within-subjects factors, and Sex and group (patients/controls) as between-subjects factors. Mean accuracy is shown in Figure 1. The ANOVA revealed a significant Ear by Task interaction, $F(1, 36) = 27.90$, $p < 0.001$, $\eta^2 = 0.44$, indicating the expected REA and LEA for the linguistic and prosodic tasks respectively. Moreover, there was an interaction between Ear and Group, $F(1, 36) = 6.67$, $p < 0.05$, $\eta^2 = 0.16$. The 3-way interaction between Task, Ear, and Group was also significant, $F(1, 36) = 27.51$, $p < 0.001$, $\eta^2 = 0.16$. The 3-way interaction was still significant when YMRS and HAM-D scores were included as covariates ($F(1, 34) = 7.45$, $p < 0.01$, $\eta^2 = 0.18$). To investigate the nature of the 3-way interaction, accuracy scores for the linguistic and

prosodic tasks were subjected to two separate ANOVAs with Ear (left/right) as within-subjects factors, and Sex and Group (patients/controls) as between-subjects factors. The analyses revealed a significant interaction between Ear and Group for the prosodic task ($F(1, 36) = 25.70$, $p < 0.001$, $\eta^2 = 0.42$), but not for the linguistic task ($F(1, 36) = 1.47$, $p = 0.23$, $\eta^2 = 0.39$). Post-hoc paired *t*-tests (Bonferroni) revealed significantly higher accuracy rates for the left ear in the prosodic task in healthy controls (LE accuracy: 79.93 ± 7.40, RE accuracy: 60.34 ± 14.25, $t(17) = 5.66$, $p = 0.0003$). In contrast, BD patients showed the opposite with higher RE accuracy rate in the prosodic task (71.34 ± 12.67, LE accuracy: 61.62 ± 20.12). However, this difference only approached significance ($t(21) = 2.22$, $p = 0.04$, not significant after Bonferroni correction). For the linguistic dichotic listening task, both healthy controls (75.00 ± 14.79, LE accuracy: 58.64 ± 21.70, $t(17) = 3.56$, $p = 0.002$) and BD patients (72.47 ± 7.17, LE accuracy: 62.63 ± 12.02, $t(21) = 3.25$, $p = 0.004$) demonstrated higher RE accuracies.

Post-hoc unpaired *t*-tests for the prosodic task revealed significantly higher accuracy rates for the left ear in healthy controls than BD patients ($t(38) = 3.66$, $p = 0.0008$). In contrast, accuracy for the right ear was significantly lower in healthy controls than for BD patients in this task ($t(38) = 2.58$, $p = 0.014$). There were no significant group differences in left and right ear accuracy scores for the linguistic task (all *ts* < 0.74, n.s.).

To investigate potential medication effects, mean accuracy scores of only BD patients were subjected to a 2 × 2 × 2 × 2 split-plot ANOVA, with Task (linguistic/prosodic) and Ear (left/right) as within-subjects factors, and Sex and Antidepressants (drug users: n = 8, non-users: n = 14) as between-subjects factors.

Neither the main effect of Antidepressants nor any interaction with this factor was significant (all $F < 0.85$, n.s.). Similarly, the same ANOVA did not reveal any effects when Antipsychotics (drug users: n = 12, non-users: n = 10) was used as a between-subjects factor (all $F < 1.28$, n.s.).

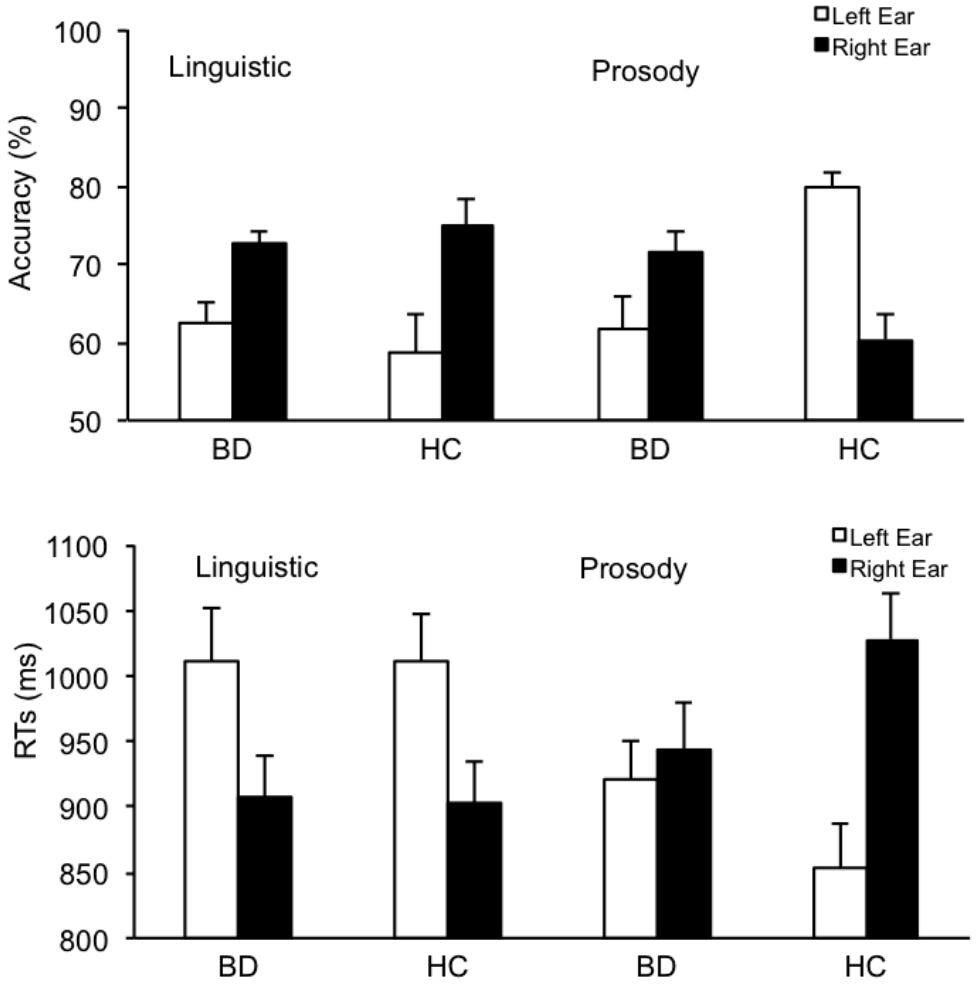

Figure 1. Correct responses (%) and response times (ms) to stimuli presented to the left ear (white bars) and to the right ear (black bars) for bipolar disorder (BD) patients and healthy controls (HC). Error bars are mean standard errors. The results for the linguistic dichotic listening task are shown on the left and those for the prosodic dichotic listening task are shown on the right.

3.2 Response times

Mean response times were subjected to a split-plot ANOVA. Mean response times are shown in Figure 1. The interaction between Task and Ear was significant ($F(1, 36) = 35.06$, $p < 0.001$, $\eta^2 = 0.49$) with an LEA in the prosodic dichotic listening task and an REA in the linguistic dichotic listening task. The interaction between Task, Ear, and Group was also significant, ($F(1, 36) = 5.24$, $p < 0.05$, $\eta^2 = 0.13$). Similar to the accuracy data, median response times were also subjected to two separate ANOVAs, one for each task. Again, the Ear by Group interaction was only significant in the prosodic dichotic listening task ($F(1, 36) = 8.53$, $p < 0.01$, $\eta^2 = 0.19$) and not the linguistic task ($F(1, 36) = 0.13$, $p = 0.91$, $\eta^2 = 0.0004$). Post-hoc paired *t*-tests revealed a faster LE response times for the prosodic task in healthy controls (853 ± 148, RE response times: 1028 ± 150, $t(17) = 4.70$, $p = 0.0002$), but not in BD patients (922 ± 131, RE response times: 945 ± 167, $t(21) = 0.65$, n.s.). In contrast, both healthy controls (902 ± 137, LE response times: 1012 ± 147, $t(17) = 3.16$, $p < 0.006$) and BD patients (907 ± 145, LE response times: 1011 ± 192, $t(21) = 2.62$, $p = 0.016$) revealed faster RE response times for the linguistic task. Post-hoc unpaired *t*-tests did not reveal any significant group differences in response time for the left and right ear in both the linguistic and prosodic tasks (all *ts* < 1.65, n.s.).

To investigate potential medication effects on response times, median response times of BD patients only were subjected to a 2 × 2 × 2 × 2 a split-plot ANOVA, with Task (linguistic/prosodic) and Ear (left/right) as within-subjects factors, and Sex and Antidepressants (drug users: n = 8, non-users: n = 14) as between-subjects factors. There was no significant main effect of Antipsychotics, nor any interaction with this factor (all $F < 1.11$, n.s.). Again, the same ANOVA did not reveal any effects when

Antipsychotics (drug users: n = 12, non-users: n = 10) was used as between-subject factor (all $F < 1.37$, n.s.).

4. Discussion

The results of the present study revealed atypical functional hemispheric asymmetries in emotional prosody in euthymic BD patients for both accuracy and response time. For the processing of emotional prosody, healthy controls and euthymic BD patients differed significantly. In contrast to controls, BD patients failed to show the expected LEA. In the linguistic task both groups revealed pronounced REA. The LEA for the prosodic dichotic listening task and REA for the linguistic dichotic listening task in healthy controls is in accordance with several previous findings (Bryden and MacRae, 1989; Grimshaw et al., 2003; Najt et al., 2012) and further supports the robustness of the dichotic listening paradigm.

According to the structural model of dichotic listening (Kimura 1967), the dominant hemisphere (i.e., left hemisphere for verbal processing and the right hemisphere for processing prosody) has direct access to stimuli presented to the contralateral ear, whereas stimuli presented to the subdominant ear have to take the indirect pathway passing through the opposite hemisphere and the corpus callosum because the weaker ipsilateral pathways are blocked or inhibited under dichotic stimulation. According to this model, reduced ear advantages in dichotic listening can occur in two different ways: (1) the dominant hemisphere is less superior because of structural and functional abnormalities, and/or (2) an increase in interhemispheric interaction, allowing the inferior hemisphere to partly compensate dysfunctional processing of the dominant hemisphere. However, the latter is rather unlikely to

explain the results of the current study because one would expect both the linguistic and prosody dichotic listening task to be similarly affected. Also, given the frequently observed negative correlation between size and integrity of the corpus callosum and the degree in dichotic listening laterality (e.g., Westerhausen et al., 2006), the recently reported reduced white matter integrity in interhemispheric tracts (including the corpus callosum) in both symptomatic (e.g., Sarrazin et al., 2014) and euthymic BD patients (Lloyd et al., 2014), should rather result in a reduction of interhemispheric croasstalk and an increase in dichotic listening laterality.

The results of the current study are in line with Mitchell et al. (2004), who found atypical low activation in the right hemisphere (i.e., inferior frontal and superior temporal gyri, and amygdala) of BD patients, as compared to healthy controls, while listening to emotional prosody. This finding was interpreted by the authors as a reduced capacity to process emotional prosody in BD patients. However, given that Mitchell et al. (2004) did not control for mood state, it was unclear whether atypical functional brain organization, and atypical right hemispheric functioning in particular, only occurs during manic/depressive mood states or also applies to euthymic states in BD patients.

In fact, depressive and manic states in BD associated to atypical functional hemispheric asymmetries are thought to involve dysregulation of the behavioral approach system (Depue and Iacono, 1989; Fowles, 1993; Johnson, 2005). This system is assumed to regulate appetitive motivation and goal-directed behavior in response to signals of reward (Gray, 2001), predicting left prefrontal functional hemispheric asymmetry during mania. Supporting the association between enhanced approach and hypomanic BD, an increased behavioral approach system sensitivity

and experiences of goal- striving and attainment events predicted future manic symptoms in BD patients (Johnson et al., 2000; Meyer et al., 2001; Nusslock et al., 2007; Salavert et al., 2007). However, although pathological positive and negative emotional states in BD have been linked to atypical functional hemispheric asymmetry, the findings of the current study suggests that atypical functional hemispheric asymmetries, especially involving right hemisphere functioning, can still be found in BD regardless of mood episodes. The present study addressed this issue by studying functional hemispheric asymmetries in BD patients during the euthymic phase. The finding of a significantly reduced LEA in emotional prosody in euthymic BD patients supported the idea that an altered functional brain organization, and especially atypical right hemisphere functioning, is a general correlate of BD, which is independent of emotional state.

It is important to note that an atypical functional hemispheric asymmetry for emotional prosody, and right hemisphere dysfunction in particular, was also found in healthy subjects with BD-related personality traits. Using the same prosodic and linguistic dichotic listening tasks as in the present study, a similar reduced LEA in the prosodic task has been found in healthy males who are high in impulsive non-conformity, a hypomanic-related personality trait (Najt et al., 2013). Healthy subjects with low impulsive non-conformity scores showed the typical LEA in this task. In addition, a typical REA was found in the linguistic task, irrespective of this personality trait. The similarities in functional hemispheric asymmetries between the euthymic BD patients of the present study and healthy men high in impulsive non-conformity, suggests that BD-related personality traits can already be linked to atypical right hemisphere functioning in emotional prosody, even when not exceeding

the pathological level. The idea of a vulnerability marker in BD has been further supported by a meta-analysis comparing euthymic BD and their first-degree healthy relatives, who showed similar cognitive impairments, albeit to a lesser degree (Arts et al., 2008).

The conclusion that right hemispheric functioning is especially affected is also supported by the finding of a preserved REA in the linguistic dichotic listening task in euthymic BD patients which is virtually identical to that shown in healthy controls. This parallels the study of Bruder et al. (1994), that found the expected REA in a consonant-vowel dichotic listening task testing BD patients in both manic and euthymic states. The preserved left hemispheric functioning is also in line with other findings in symptomatic BD patients, who showed a typical REA in a consonant-vowel dichotic listening task during mania and depressive mood states (e.g., Bruder et al., 1989; Bruder et al., 1992). So far, there has only been one dichotic listening study (Kaprinis et al., 1995) that reported a reduced REA in a verbal dichotic listening task in manic BD patients. However, the finding of atypical left hemispheric functioning by Kaprinis et al. (1995) might be related to the presence of positive symptoms of psychosis (e.g., hallucinations or delusions) in BD patients taking part in this study. Overall, these findings by Kaprinis et al. (1995) and Bruder et al. (1989,1992) toeghether with the present findings suggest that processes that rely predominantly on the right hemisphere (i.e. emotional processing) are especially affected in BD regardless of mood symptoms. Left hemisphere functions, such as linguistic processing, seem to be largely preserved. The reason why the right hemisphere is affected remains unclear. However, it is important to note that the right hemisphere is especially involved in processing emotion, regardless of valence (Borod et al., 1998).

Such atypical functional hemispheric asymmetries affecting right hemispheric emotional networks may underlie specific processes that foster the maintenance of intense emotion perception, even during asymptomatic phases.

In line with previous neuroimaging studies on euthymic BD patients (e.g., Wessa et al., 2007; Robinson et al., 2008; Chen et al., 2010; Keener et al., 2012) our results suggest that right hemisphere dysfunction is not necessarily related to BD symptoms. In fact, it seems rather unlikely that atypical functional hemispheric asymmetries are the origin of clinical symptoms. It could also be that atypical functional hemispheric asymmetries represent a compensatory strategy of the brain in order to reduce BD symptoms. If this were to be true, the question arises as to how such an adaptive strategy is achieved. One explanation is that hyperactivation of the right hemisphere, as frequently reported in BD (e.g., Wessa et al., 2007; Robinson et al., 2008; Chen et al., 2010), might simply indicate an increased effort of the right hemisphere in emotion processing (Morris et al., 2012).

This study had the limitation that the patients group was quite heterogenous as with regard to their medication. This was addressed by comparing subsamples of patients. Although the results did not reveal any evidence that antipsychotics and antidepressants had any effects, this finding needs to be interpreted with caution, given that the current sample was relatively heterogeneous with respect to medication subclasses. Another limitation is that the present study did not test symptomatic BD patients which may weakns the conclusion of right hemispheric dysfunction as a vulnerability marker. However, it should be noted that symptomatic patients have been already tested in previous studies (Bruder et al., 1989; Bruder et al., 1992;

Kaprinis et al., 1995) and that investigating euthymic BD patients was critical for testing our hypothesis.

In sum, BD patients showed atypical functional hemispheric asymmetries characterized by a significantly reduced LEA in emotional prosody, which indicates atypical right hemisphere functioning in emotion processing. Left hemispheric functioning seems not to be affected in these patients. The results further indicate that the current mood state of BD patients does not account for these findings, as atypical right hemispheric functioning was present in patients that were symptom free at the time of testing. Given that similar findings have recently been reported in healthy men loading highly on hypomanic-related personality traits, the results further suggest that atypical functional hemispheric asymmetries in predominantly right hemisphere functions are characteristic of the BD spectrum. Finally, the present study supports the view that the dichotic listening paradigm is a useful tool to characterize functional brain organization as a risk factor in various neuropsychiatric disorders.

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